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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/496,391	02/02/2000	James D. San Antonio	SAN01-NP001	6140

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EXAMINER	
CANELLA, KAREN A	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 03/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/496,391	SAN ANTONIO ET AL.	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ____ MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *10-63 and 70-89* is/are pending in the application.

4a) Of the above claim(s) *10-63 and 70-75* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *76-89* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-9 and 64-69 have been canceled. Claims 76-89 have been added. Claims 10-63 and 70-75, drawn to non-elected inventions, are withdrawn from consideration. Claim 76-89 are under consideration.

Text of sections of Title 35, US code not found in this action can be found in a previous action.

Claims 76-89 are rejected for incorporation of new matter. the specification and claims as filed provide adequate written description for peptides having high affinity for glucosamino glycan and proteoglycan, wherein the peptide structure comprised the disclosed sequence motifs. the instant claims have been amended to recite only a synthetic peptide comprising said sequence motifs Thus, the genus of peptides claimed encompass proteins which minimally comprise said sequence motifs but do not exhibit proteoglycan or glucosamino glycan affinity. It is well known in the art that proteins are folded 3-dimensional structures, the function and stability of which are directly related to a specific conformation (Mathews and Van Holde, Biochemistry, 1996, pp. 165-171). In any given protein, amino acids distant from one another in the primary sequence may be closely located in the folded, 3-dimensional structure (Mathews and Van Holde, Biochemistry, 1996, pp. 166, figure 6.1). The specific conformation of a protein results from non-covalent interactions between amino acids, beyond what is dictated by the primary amino acid sequence. A different amino acid sequence surrounding a fragment of the MMAC1 protein can potentially radically alter the three dimensional structural environment in which the given fragment is located (Matthews, B. "Genetic and Structural Analysis of the Protein Stability Problem") thus, a genus of proteins which minimally comprise the recited sequence motifs would not be guaranteed the function of glucosamino glycan binding.

Thus, the genus of peptides claimed is variant encompassing proteins which minimally comprise the disclosed motifs but having widely different function. the disclosure of a peptide having high affinity for glucosamino glycan and proteoglycan having the disclosed sequence motifs does not adequately describe the genus claimed because members of the genus can have different functional attributes from binding glucosamino glycan and proteoglycan and can include members which do not bind glucosamino glycan and proteoglycan. One of skill in the

art would reasonable conclude that the new amended claims encompassed a larger and more varied genus than what was present if the originally filed specification and claims. Accordingly, the claims are rejected for incorporation of new matter.

Claims 82 and 89 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 82 and 89 are vague and indefinite in the recitation of "a single cystiene residue is contained in said synthetic peptide at a position within three amino acid residues of the N-terminus of the C-terminus of said synthetic peptide". It is unclear if the single cysteine residue is an "X" of the recited segments, or if said cysteine residue is in addition to the recited segments. applicant argues that the claims have been re-written to specifically define the position of the cysteine residue in terms of the peptide terminus and not the cardin sequence, however, the instant claims 82 and 89 do not exclude the cysteine residue being part of the "X" of the cardin site which is located within three amino acids of the N-terminus or the C-terminus

Claim 88 is rejected under 35 U.S.C. 103(a) as being unpatentable over deBoar et al (The Journal of Biological Chemistry, 1992, Vol. 267, pp. 2264-2268, cited in a previous action) in view of Cardin et al (Arteriosclerosis, 1989, vol. 9, pp. 21-13, reference AD of the IDS submitted March 31, 2003).

It is noted that new claim 88 comprises the same subject matter as old claim 68.

Claim 88 is drawn to a synthetic concatameric peptide wherein the sequence of amino acid residues of said peptide is represented by at least two segments selected from the group consisting of XBBBXXBX, XBXXBBBX, XBBXBX and XBXBBX wherein said peptide does not comprise only XBBBXXBX, XBXXBBBX, XBBXBX or XBXBBX., each segment is separated from adjacent segments by at least two amino acids, each B residue is independently selected from the group consisting of Arg and Lys, and each X is independently selected from Ala or Gly.

DeBoar et al teach a synthetic peptide comprising residues Lys348 to Arg361 of vitronectin. DeBoar et al teach that these residues include the consensus sequences for glycosaminoglycan recognition (Figure 5). DeBoar et al teach other peptides which do not include both Cardin sites as indicated by peptides 1 and 3 in figure 5, and that the peptide 2 containing both Cardin sites was the most efficient inhibitor of the binding of the vitronectin thrombin-anti-thrombin complex to human umbilical vein endothelial cells (page 2267, second column, lines 26-35 under the heading "Discussion"). DeBoar et al teach that peptide inhibition of the binding of the vitroncetin-thrombin-anti-thrombin complex to the endothelial cells was correlated to the ability of said peptides to directly bind heparin (page 2267, second column, bridging sentence). The Cardin sites in said peptide taught by DeBoar et al are separated by at least one amino acid and the "B" residues are arginine or lysine, however, the X residues are not confined to alanine or glycine. Thus deBoar et al do not teach the instant peptide wherein X is alanine or glycine.

Cardin et al teach the Cardin sites of XBBBXXBX and XBBXBX (abstract). Cardin et al teach that the "B" residues represent a relative probability of basic amino acids and that the "X" residue represents a relative probability of non-basic amino acids in heparin-binding proteins. In the legend for Table 4 (Cardin et al), the "X" residues are broken down statistically to percentage aromatic, acidic and basic. It is noted that adding the percentages of aromatic, acidic and basic for any position gives a percentage far less than 100. Therefore, it is easily deduced that the remainder of the amino acid at the "X" position are neutral or hydrophobic in heparin binding consensus sequences..

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to substitute a "A" or a "G" for any of the positions designated as "X" in the Lys348 to Arg361 peptide as taught by deBoar et al.

One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Cardin et al who break down the "X" residue into relative probabilities of related amino acid residues, and the indication that heparin binding consensus sequences have "X" residues that are dominantly neutral or hydrophobic, rather than aromatic, acidic or basic, because these residues represents a small percentage of the "X" residues, and

thus, most consensus sequences would be represented by neural or hydrophobic sequences at the "X" positions.

Applicant argues that the rejection is faulty because the claim recites four motifs rather than two motifs. this has been considered but not found persuasive. the claims recited four motifs in a Markush group , with the specific limitation that the synthetic peptide is at least two of the members of the group. It is a basic tenant of patent examination, that the disclosure of a single species anticipates the claim to a genus. thus disclosure of a peptide comprising two of the recited groups would anticipate the broader genus claims. Applicant argues that it would not be obvious to substitute "A' or "G" in the positions designated as "X" in the Lys348 to Arg361 peptide taught by deBoar. this has been considered but not found persuasive. It is common convention to use "X" to signify that any amino acid can occupy the indicated residue. as stated above, Cardin et al specifically teach that "X" residue represents a relative probability of non-basic amino acids in heparin-binding proteins. In the legend for Table 4 (Cardin et al), the "X" residues are broken down statistically to percentage aromatic, acidic and basic. for purpose of explanation consider the motif XBBBXXBX wherein the first X is X1, and the second X is X2, etc. The legend for table 4 it is indicated that X1 was analyzed to be 14% basic, 3% acidic and 6% aromatic, X2 was found to be 0% basic, 3% acidic and 11% aromatic, X3 was analyzed to be 0% basic, 7% acidic and 3% aromatic, X4 was analyzed to be 21% basic, 3% acidic and 6% aromatic. A simple perusal of the listing leads one of skill in the art to conclude that the basic, acidic and aromatic residues encompassed by X1 through X4 are a minor part of the composition of X1 to X4. Elementary mathematics indicates that 77% of amino acids residues in position X1 are not basic, acidic or aromatic; 86% of the amino acid residues at X2 are not basic, acidic or aromatic ; 90% of X3 are not basic, acidic or aromatic; and 90% of X4 are not basic, acidic or aromatic. Neither alanine nor glycine is basic, acidic or aromatic.

Applicant argues that the ability of the peptide of the invention of bind with heparin is correlated with the ability of the peptide to conform to an alpha-helix on contact with heparin, and that the peptides of the present invention adopt an alpha-helix only upon interaction with heparin. applicant argues that the concept of alanine acting as a alpha-helix stabilizer was not recognized by DeBoar or Cardin. this was considered but not found persuasive. applicant is arguing limitations which are not part of the instant claims which are drawn only to synthetic peptides

having the recited motifs and not to any peptide having a specific activity upon binding to heparin.

Applicant argues against the use of the DeBoar reference arguing that DeBoar mis-states the relationship between his peptide cell binding datat and the data of Tomassini. this has been considered but not found perusasive becuse DeBoar teaches that the binding of VN-TAT to HUVEC was inhibited by heparin and by an antibody directed toward the heparin binding domain of vitronectin. DeBoar unequivocally teaches that the Lys345 to Arg361 peptide taken from the heparin binding domain of vitronectin. Because the heparin binding domain could be expected to bind to heparin, a peptide having a sequence taken from the heparin binding domain, which can antagonize the binding of VN-TAT to HUVEC, said binding also known to be antagonized by heparin, would also be expected to bind to heparin. the conclusion of DeBoar is that the Lys345-Arg361 peptide binds to heparin.

All other rejections and objection as set forth in the previous office action are withdrawn in light of applicants arguments and amendments.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10 a.m. to 9 p.m. M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on (571)272-0871. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.
Art Unit 1642
03/22/04

KAREN A. C... PRIMARY EXAMINER